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09/544,045	04/06/2000	Brian Lee Sauer	OMRF 178	8128

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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/544,045	Applicant(s) Sauer et al.
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 26, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above, claim(s) *50-65* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Amendments to the claims in Paper No. 15, filed June 26, 2002 have overcome the rejection of the claims under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn.

2. Amendments in Paper No.15 have overcome the rejection of the claims under 35 USC 102 and 35 USC 103 in the previous office action, and the rejections are withdrawn.

3. Applicant's arguments with respect to claims 1-49 have been considered but are moot in view of the new ground(s) of rejection.

Election/Restriction

4. Claims 50-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-VII, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Specification

5. A reply to the objection to the specification regarding the sequence rules was made as part of the submission of Paper No. 15. Unfortunately, the practice of "decontamination" of official mail to the PTO has resulted in the destruction of the sequence disk. A new disk is

required to process the submission. Therefore, a new disk is requested to be submitted at this time. (see the attached sequence problem report)

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-47 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the practice of the method *in vitro*, does not reasonably provide enablement for in an animal, which constitutes gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim is drawn to a method of identifying variant recombinases that mediate recombination at variant recombination sites. While applicants have shown the practice of the method *in vitro*, they have not demonstrated any practice of the method in an animal. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve demonstration of the ability to practice the method in an animal.

b- The only working examples presented in the instant specification are done *in vitro*, and no examples of practice of the invention are presented in an animal.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

f- The relative skill of those in the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no

conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

g- The art is unpredictable, since a negative result which may result from any one of the above mentioned "problems" cannot be explained by the teachings of those of skill in the art. The instant claims and specification must therefore provide the necessary teachings to enable the use of the instant claimed method in an animal. Such teachings are not found in the instant claims or specification.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-6 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al.

Miller et al. teach (see especially the introduction, figures and materials and methods):

A) a method bringing into contact a mutant recombinase

B) with a pair of mutant recombination sites or a pair of wild type recombination sites, which are comprised on first and second nucleic acid sequences (constructs)

C) comparing the activity of the mutant recombinase on the mutant recombination sites to the activity of the wild type recombinase on the mutant recombination sites

D) the mutant recombination sites may have identical sequences

E) the mutant recombination sites may not recombine with the wild type recombination sites

E) the mutant recombination sites may have significant reduction in recombination frequency with wild type recombinase

F) the constructs with the recombination sites alter the expression of the reporter gene when the recombination sites are recombined.

10. Claims 1-6 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Serre et al.

Serre et al. teach (see especially the introduction, figures and materials and methods):

A) a method bringing into contact a mutant recombinase

B) with a pair of mutant recombination sites or a pair of wild type recombination sites, which are comprised on first and second nucleic acid sequences (constructs)

C) comparing the activity of the mutant recombinase on the mutant recombination sites to the activity of the wild type recombinase on the mutant recombination sites

D) the mutant recombination sites may have identical sequences

E) the mutant recombination sites may not recombine with the wild type recombination sites

E) the mutant recombination sites may have significant reduction in recombination frequency with wild type recombinase

F) the constructs with the recombination sites alter the expression of the reporter gene when the recombination sites are recombined.

11. Claims 1-6 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ackroyd et al.

Ackroyd et al. teach (see especially the introduction, figures and pages 637-638):

A) a method bringing into contact a mutant recombinase

B) with a pair of mutant recombination sites or a pair of wild type recombination sites, which are comprised on first and second nucleic acid sequences (constructs)

C) comparing the activity of the mutant recombinase on the mutant recombination sites to the activity of the wild type recombinase on the mutant recombination sites

D) the mutant recombination sites may have identical sequences

E) the mutant recombination sites may not recombine with the wild type recombination sites

E) the mutant recombination sites may have significant reduction in recombination frequency with wild type recombinase

F) the constructs with the recombination sites alter the expression of the reporter gene when the recombination sites are recombined.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-30 and 32-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Serre et al. or Miller et al. or Ackroyd et al. in view of US 5,677,177 (of record).

The claims are drawn to a method to identify a mutant recombinase, where the mutant recombinase is tested for activity on wild type and mutant recombination sites. The mutant recombination sites (first and second sites) are on a first nucleic acid and the wild type recombination sites (third and fourth) are on a second nucleic acid. The wild type and mutant recombination sites are linked to reporter genes. The mutant recombinase has greater activity with the mutant recombination sites than with the wild type recombination sites, and the wild type recombinase has lowered activity with the mutant recombination sites. The mutant recombination sites may be identical, and the wild type recombination sites may be identical. The first and second nucleic acids contain structural genes. The recombination of the first and second recombination sites alters expression of the first reporter and recombination between the

third and fourth recombination sites alters expression of the second reporter. The reporter gene expression may be activated or inactivated by the removal of a spacer in, or near the reporter which blocks expression of the reporter gene. The reporter gene may be activated or inactivated by an inversion of part or all of the reporter gene. The reporter gene may be excised from the construct. The first and second nucleic acid sequences may be connected by a preselected DNA segment. The mutant recombinase may be further tested for activity on one or more additional recombination sites. The recombination reaction may occur *in vitro* or may occur in a cell which may be in a prokaryotic cell or a eukaryote cell. The eukaryotic cell may be in a plant or a mammal.

Each of Serre et al. or Miller et al. or Ackroyd et al. taught the invention as described above in the rejections under 35 USC 102.

Each of Serre et al. or Miller et al. or Ackroyd et al. did not teach that the first and second nucleic acids may be linked by a DNA segment, nor the deletion or excision of the reporters or spacers, nor inversion of the reporters to switch on or switch off expression of the reporters. Also not taught was the performance of the method in a eukaryotic cell.

US 5,677,177 taught (see especially the abstract, Brief Description, figures and columns 3-8) the well known use of a recombinase to insert, invert and delete a sequence in a construct to inactivate or activate a desired gene sequence, such as a reporter, in a mammalian cell, where the cell may be in a mammal.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of each of Serre et al. or Miller et al. or Ackroyd et al. with US 5,677,177 to produce the instant invention because Serre et al. or Miller et al. or Ackroyd et al. taught the use of the method of identification of mutant recombinases in a model system, where the teachings would apply to other recombination methods. US 5,677,177 taught the general utility of use of a recombinase to insert, invert and delete sequences in a construct to inactivate or activate a desired gene sequence, such as a reporter in a mammalian cell as taught in Serre et al. or Miller et al. or Ackroyd et al. The teachings of US 5,677,177 suggests the methods taught therein have specific applicability to any recombination method.

One of ordinary skill in the art would have been motivated to combine the teachings of each of Serre et al. or Miller et al. or Ackroyd et al. with US 5,677,177 to produce the instant invention because US 5,677,177 taught the desirable and beneficial use of a recombinase to insert, invert and delete sequences in a construct to inactivate or activate a desired gene sequence, such as a reporter in a mammalian cell, where the cell may be in a mammal. The deleting, inserting and inverting activity of recombinases is well known, and US 5,677,177 taught this specific, desirable and beneficial use of a recombinase in any method involving the use of a recombinase where activation or inactivation of a gene is desired. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Serre et al. or Miller et al. or Ackroyd et al. with US 5,677,177.

Conclusion

14. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
September 1, 2002

TERRY MCKELVEY
PRIMARY EXAMINER